REMARKS

Claims 33-36, 39-41, 44, 48-52, 55-56 and 59 are pending. Claim 41 has been amended to proper dependent form. Support for this amendment can be found throughout the specification and claims as originally filed.

Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement to provide additional copies of Offices Actions which have issued in related cases previously made of record.

Objection to Claim 41

The Examiner has objected to claim 41 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Examiner asserts that the claim does not refer back in the alternative.

Responsive to the objection, claim 41 has been amended to correct the deficiency noted by the Examiner. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

Objection to Claim 44

The Examiner has objected to claim 44 as being in improper form because of multiple dependent claim 41. Accordingly, as discussed above, claim 41 has been amended such that it has proper dependency and thus, the the present objection to claim 44 should now be moot.

Rejection of Claims 33-36, 39-41, 44, 48-52, 55-56 and 59 Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 33-36, 39-41, 44, 48-52, 55-56 and 59 as being unpatentable over WO 01/85798 in view of US 5,869,057. The Examiner relies on WO 01/85798 for teaching human monoclonal antibodies that bind to the macrophage mannose receptor (present on dendritic cells) conjugated to a tumor antigen. The Examiner acknowledges that the '798 publication does not teach the use of βhCG as a tumor antigen, but asserts that the '057 patent teaches the use of βhCG as an antigen that "is

detectable on the surface of all tumor cells and could be used in immunization against βhCG and an antimetastasis treatment." The Examiner thus concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ βhCG as a tumor antigen as taught by the '057 patent into a molecular conjugate comprising a human monoclonal antibody that binds to dendritic cells and immunostimulatory cytokine taught by the '798 publication to practice the claimed method."

Applicants respectfully traverse this rejection for at least the following reasons.

1. βhCG As Encompassed by the Claims is Not Limited to a Particular Sequence

As previously noted by Applicants, based on the teachings of the prior art at the filing date of the application, it would not have been obvious that βhCG (*i.e.*, a self protein) could successfully be used as a vaccine to induce T cell mediated immune responses when targeted via an antibody to the human MMR and when formulated without an adjuvant or immunostimulatory agent. In support of this proposition, Applicants cited, for example, Gupta *et al.*, (*J. Mol. Endocrinol.* 2001 Jun;26(3):281-7), Lund and Delves ((1998), Reviews of Reproduction 3:71-76) and Triozzi *et al.* (Ann NY Acad Sci (1993)).

In response, the Examiner asserts that Applicants' arguments based on these cited references are "irrelevant" and "misleading" because the portion of βhCG described in these references is different from the βhCG recited in the pending claims. Specifically, the Examiner asserts that:

> The claimed βhCG is derived from SEQ ID NO:20 as is defined by the specification of the instant application in p. 12. The claimed βhCG is outside of the carboxyl terminus (e.g. 1-37 amino acids) that is corresponding 61-69 of the entire hCG. Thus, Applicant's assertion based on the segment of hCG that is not recited in the claimed invention is irrelevant.

Applicants respectfully disagree. Contrary to the Examiner's assertion, the presently claimed methods are not limited to a particular βhCG sequence. Pursuant to MPEP 2111, "pending claims must be 'given their broadest reasonable interpretation consistent with the specification.'" Consistent with this principle, any βhCG peptide or fragment thereof is covered by the presently claimed methods. Indeed, the particular βhCG fragments provided in Applicants' disclosure (*e.g.*, SEQ ID NO:20) are merely representative examples of the

claimed class of βhCG peptides. Accordingly, the teachings of Gupta *et al.*, Lund and Delves and Triozzi *et al.* previously discussed by Applicants are, indeed, relevant to show that the prior art taught that βhCG required an adjuvant or immunostimulatory agent to induce an adequate vaccine effect.

2. Lund *et al.* Does Not Teach That βhCG Alone Elicits an Immune Response

As discussed above, Applicants have cited several references in support of the argument that it would not have been obvious that βhCG (*i.e.*, a self protein) could successfully be used as a vaccine to induce T cell mediated immune responses (1) when targeted via an antibody to the human MMR and (2) formulated without an adjuvant or immunostimulatory agent. The Examiner asserts that the cited references are "irrelevant" and "misleading", because the portion of βhCG described in these references is different from the βhCG enclosed by the pending claims. However, also as pointed out above, the pending claims are not limited to a particular βhCG (*e.g.*, SEQ ID NO:20), but instead read on the full βhCG antigen and any portions or variants thereof. As such, the cited references are indeed relevant, and clearly show that the prior art taught that βhCG-based vaccines must include potent carriers and adjuvants, because human βhCG antigen was well known to be "self-tolerant".

Moreover, the Examiner characterizes Lund *et al.* (Reviews of Reproduction 3:71-76 (1998)) as follows:

> Lund et al reference (also provided by Applicant) clearly discloses that the 37 amino acids from the carboxyl terminus of βhCG requires immunogenic carrier protein while the ***holo-βhCG*** enzyme does not require any adjuvant (emphasis added).

However, the actual quote from Lund *et al.* referred to by the Examiner reads as follows:

> Triozzi et al (1997) immunized non-HLA-matched human subjects with the 37 amino acid CTP covalently linked to DT. Subsequently, T cell proliferative responses could be obtained after stimulation in vitro with ***hCG holo-hormone***, but not with the CTP in the absence of a carrier (emphasis added).

The hormone referred to in the particular passage of Lund *et al.* cited by the Examiner is not "***holo-βhCG***" as indicated by the Examiner, but is instead hCG holo-hormone, which includes both the alpha and beta subunits, rather than the beta subunit encompassed by the

pending claims. As described by Lund *et al.*, hCG holo-hormone induced a T cell proliferative response in an *in vitro* assay, whereas ***CTP (i.e., amino acids 113-145 of βhCG) did not induce a T cell proliferative response in the absence of a carrier***. The fact that CTP in and of itself did not induce a T cell response further supports Applicants' arguments that the prior art taught that βhCG is not immunogenic.

The Examiner further states that:

> Moreover, Lund et al teaches that the purified ***βhCG*** in the absence of carrier protein elicits immune response (p.71, under T cell epitope) (emphasis added).

However, the actual passage from Lund *et al.* referred to by the Examiner relates to ***whole hCG***, which comprises both the alpha and beta subunits, rather than the beta subunit encompassed by the pending claims.

> ***Purified hCG in the absence of a carrier protein can elicit an antibody response in mice and rabbits, implying that one or both subunits contain appropriate helper T cell epitopes for these species***. After immunization of BALB/c mice, Rouas *et al.* (1993) were able to identify two overlapping T cell epitopes on the α-subunit (residues α50-70 and α60-80, respectively) and two distinct epitopes on the β-subunit which included the residues β1-13 and β11-22. As a part of preliminary studies aimed at developing an anti-tumour vaccine, Triozzi *et al.* (1997) immunized non-HLA-matched human subjects with the 37 amino acid CTP covalently linked to DT. Subsequently, ***T cell proliferative responses could be obtained after stimulation in vitro with hCG holo-hormone***, but not with the CTP in the absence of a carrier, suggesting that either or both of the α- and the β-subunits possess T cell epitopes able to bind to various HLA class II molecules.
>
> After immunization of BALB/c mice with an expression plasmid containing the hCGβ gene, Geissler *et al.* (1997) demonstrated that the β-subunit can induce a cytotoxic T lymphocyte (CTL) response, suggesting that the hormone also contains sequences that can bind to MHC class I molecules. Furthermore, they found that the induced CTL response could prevent the growth of a myeloma cell line transfected to express hCGβ. ***While hCGβ CTL epitopes in humans have yet to be defined, their characterization would clearly facilitate the development of an hCGβ-specific anti-tumour vaccine***. (emphasis added).

Thus, the passage relied on from Lund *et al.* does not teach that purified βhCG alone elicits immune response, as indicated by the Examiner.

Moreover, the above passage from Lund *et al.* refers to the ability of purified whole hCG to elicit an antibody response in mice and rabbits, not humans. In fact, Lund *et al.* clearly states at page 72 that "hCGb CTL epitopes in humans have yet to be defined".

3. US 5,869,057 Teaches Adjuvants are Required to Produce effective βhCG Vaccines

The Examiner asserts that "even if the claimed composition precludes any means of adjuvant in the composition, at any stages of treatment, the claimed invention is still obvious over the combination of the prior art." Specifically, the Examiner supports this position by pointing to a passage of the '057 patent which reads:

> My invention offers four primary advantages over prior art…
> Second, my invention precludes the need for ***additional adjuvants*** such as muramyl dipeptide in the final vaccine formulation (lines 54-55) (emphasis added).

Based on this, the Examiner concludes that:

> Therefore, the prior art recognizes preclusion of additional adjuvant if self and non-self recognition is established using the antigen such as βhCH and the presence of T cell immune response inducing protein carrier is achieved by the '798 publication.

Applicants respectfully disagree. Importantly, the above quotation from the '057 patent that is cited by the Examiner omits part of the text from column 11, lines 47-64 of the '057 patent. Specifically, the complete text of column 11, lines 53-56 of the '057 patent reads:

> Second, **due to the natural action of microbial products**, my invention precludes the need for additional adjuvants such as muramyl dipeptide in the final vaccine formulation. (emphasis added)

Accordingly, the '057 patent does, indeed, teach the use of adjuvants. Specifically, the '057 patent teaches that at a minimum, "microbial products" (*i.e.*, natural adjuvants) must be included to produce a therapeutically effective vaccine. The '057 patent also notes that adjuvants "must be included in the vaccine formulation in order for processing and presentation of T cell epitopes by specialized antigen presenting cells such as macrophages and dendritic epidermal cells to occur" (col. 11, lines 3-7).

Consistent with this proposition, the vaccine described in the '057 patent includes both a self antigen (*i.e.*, βhCG) and a non-self microbial product (*i.e.*, *E. coli.* heat-labile enterotoxin subunit B (LTB)), which has "natural" adjuvant properties. Thus, the '057 patent in fact teaches away from the presently claimed invention by explicitly acknowledging that at

least a microbial product (*i.e*, "natural" adjuvant) is required in order to produce an effective βhCG vaccine. In contrast, the presently claimed methods comprise a composition formulated without any adjuvants or immunostimulatory agents (including microbial products or other foreign T helper epitopes) containing an anti-MMR antibody linked to βhCG.

4. The Prior Art Does Teach Adjuvants are Required for an Effective βhCG Vaccine

Prior to the filing of the present application, one of ordinary skill would not have been motivated to have formulated a βhCG vaccine comprising βhCG linked an antibody against the human MMR to generate an immune response without an adjuvant or immunostimulatory agent, as claimed, since it was well known that antibodies are not microbial gene products, and do not have microbial adjuvant properties, such as helper T cell epitopes. Specifically, as previously argued by Applicants, the prior art taught that hCG-based vaccines must include potent carriers and adjuvants because human βhCG antigen was well known to be "self-tolerant". For example, as taught by Gupta *et al.*, (*J. Mol. Endocrinol.* 2001 Jun;26(3):281-7; enclosed herewith as Appendix A):

> βhCG, being a 'self' molecule, is ***required*** to be linked to protein carrier molecules to render it immunogenic. Protein carriers have limitations and can be substituted by a combination of helper T-cell peptides (Mandokhot *et al.*, 2000) (emphasis added).

This is supported by Lund and Delves ((1998), Reviews of Reproduction 3:71-76; enclosed herewith as Appendix B), which teaches that:

> [t]he glycoprotein hormones are 'self' antigens. Although normally expressed only during pregnancy, it appears that hCG is very effective at establishing immunological tolerance. There are hardly any reports of circulating autoantibodies to the hormone being detected in humans, even in patients with a history of recurrent spontaneous abortion (Tulppala *et al.*, 1992). However, it is also clear that this tolerance is not absolute, because when it is ***administered coupled to a potent carrier and in the presence of adjuvant, hCG can break tolerance and elicit an immune response*** (emphasis added).

(paragraph spanning pages 74-75). Further evidence that the prior art believed the only relevant form of βhCG vaccine was one which was linked to an immunogen carrier and/or included an adjuvant, is provided by Triozzi *et al.* This reference describes conjugates

of βhCG-CT coupled to diphtheria toxoid and combined with the adjuvant, muramyl dipeptide and a vehicle, squalene/mannide monooleate (Ann NY Acad Sci (1993); enclosed as Appendix C).

Importantly, even the patent cited by the Examiner, US 5,869,057, teaches that it is necessary to link a "self" gene product (βhCG epitope) to a microbial (non-self) gene product (*e.g.*, a prokaryotic helper T cell epitope, such as heat-labile entertoxin B subunit (LTB)), since it is the "natural adjuvant properties of microbial gene products" that are used to illicit an immune response and produce a therapeutically effective vaccine.

Further, it was known in the art prior to the filing of the present invention that self-proteins, such as βhCG, in and of themselves do not typically activate a T cell response. Specifically, as described in Dalum *et al.* (*Mol Immunol.* 1997 Nov-Dec; 34(16-17):1113-20); enclosed as Appendix D),

> Normally, the presentation of self peptides ***does not lead to stimulation of T cells*** because of tolerance toward MHC associated epitopes derived from the self proteins. A major reason for the non-responsiveness of self reactive B cells could be the lack of direct T-cell help. ***Accordingly, to make self Ags immunogenic, immunostimulatory Th epitopes have been coupled to chemically to the Ags*** (Talwar *et al.,* 1994; Sad *et al.*, 1993; Steinhoff *et al.,* 1994) (emphasis added).

Accordingly, the prior art does, indeed, teach that adjuvants are required for an Effective βhCG vaccine.

5. Applicants Were the First to Develop an Effective βhCG Vaccine, Which Does Not Require Any Adjuvants or Other Agents

Applicants were the first to show that by linking βhCG to an anti-MMR-antibody, the presently claimed conjugates were capable of presenting the antigen *via* both MHC class I and class II pathways. Specifically, βhCG is targeted to the MMR and processed through both MHC class I and class II pathways. Thus, antigen-specific CTLs (*e.g.*, $CD8^+$ T cells) are activated, as well as other important effector T cells, including helper T cells (*e.g.*, $CD4^+$ T cells), resulting in a completely different response (*i.e.*, cytolytic T cells) than that taught in the prior art (*i.e.*, generation of blocking antibodies).

For at least the foregoing reasons, the presently claimed methods are patentable in view of the cited references, as well as knowledge available in the art prior to the filing of the present application. Moreover, Applicants respectfully submit that the findings which form the basis of the present invention were completely unexpected and would not have been obvious to one of ordinary skill in the art. Accordingly, Applicants respectfully request that this section 103 rejection be reconsidered and withdrawn.

CONCLUSION

If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. CDJ-301RCE3.

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